REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants have added claim 11 directed to the intermediate compound fluconazole monohydrate having a melting point of 139° to 140° C prepared by the process defined in claim 1. Antecedent basis for new claim 11 may be found in Examples 1 and 4. Thus claims 1 through 11 are now in the application and are presented for examination.

Applicants appreciate the Examiner's indication that claims 9 and 10 are directed to allowable subject matter and that these claims would be allowable if written in independent form. Applicants ask, however, that the Examiner reconsider her rejection of claims 1 through 8 in view of the information presented hereinbelow including the showing in the Declaration Under 37 CFR 1.132 that accompanies this amendment.

The Examiner indicates that all of the remaining claims are prima facie obvious in view of the combination of US Patent 5,371,101 to ITOH et al, GU et al, Journal of Pharmaceutical Sciences, US Patent 5,707,976 to KREIDL et al, and US Patent 5,872,258 to CLIVE et al. Applicants note, first of all, that claim 1 is directed to the preparation of fluconazole monohydrate from

the known silyl ether starting material of the Formula (II). None of the four references applied by the Examiner deals with the preparation of fluconazole monohydrate.

ITOH et al discloses compounds that are not at all structurally similar to fluconazole. Fluconazole contains two 1,2,4-triazol-1-yl moieties and is a bis compound. The ITOH et al compounds can contain only one, but not two 1,2,4-trriazol-1-yl moieties, and so are not bis compounds and are structurally very different from fluconazole. In addition the ITOH et al compounds include on one, but not on both, of the five-membered heterocyclic rings, an oxo substituent bonded to a carbon atom within the ring. As a result the ITOH et al 5-membered heterocyclic ring bearing the oxo substituent contains only one carbon-nitrogen double bond within the ring. Fluconazole contains two 1,2,4-triazole rings and no oxo substituent on either ring. Both of the 1,2,4-triazole rings of fluconazole of course contain two carbon-nitrogen double bonds. Furthermore the ITOH et al compounds contain a substituent R^3 bonded to one of the heterocyclic nitrogen atoms in the 5-membered heterocyclic ring containing only one carbon-nitrogen double bond. That substituent R^3 is defined in ITOH et al in claim 1 as an optionally substituted aliphatic or aromatic hydrocarbon residue or an optionally substituted aromatic heterocyclic group. There is no such substituent bonded to either of the 1,2,4-triazole rings of fluconazole. Thus the compounds of ITOH et al are structurally far removed from those of the present invention and are not analogous to

those of the present invention. Thus ITOH et al does not disclose the hydrolysis of a starting material that is analogous to Applicants' starting compound of the Formula (II) and so the reference provides no basis to reject any claim now in the case as obvious under 35 USC 103.

Applicants realize that substituent R4 of the ITOH et al compounds of the Formulae (I) and (VII) may stand for a trimethylsilyl group which etherifies the hydroxy group bonded to the chain between the rings. Applicants also realize that the trimethylsilyl group may be removed from the compound of the Formula (VII) by hydrolysis. Here is perhaps the only similarity between the presently claimed process and the ITOH et al disclosure. However, the hydrolysis product disclosed in ITOH et al is not a monohydrate; no mention is made of monohydrate formation and no mention is made of either characterizing or isolating a monohydrate. See Working Example 1 in col. 42 of ITOH et al as well as col. 6 and 7 which disclose the hydrolysis of the compounds of Formula (VII) to the compounds of Formula (X) with no mention of monohydrate formation. So not only are the Formula VII and X compounds in ITOH et al difference from fluconazole silyl ether and fluconazole, but furthermore there is no indication of monohydrate formation. Thus ITOH et al discloses hydrolysis of a silyl ether starting material, but nowhere is there disclosure of specific formation of a monohydrate nor are there any of the special dehydrating steps (a) through (d) to obtain crystal modifications.

Applicants are able to obtain the key intermediate fluconazole monohydrate in high purity having a melting point of 139° to 140° C by hydrolysis of the starting trimethylsilylether of the Formula (II). Again, there is no disclosure in ITOH et al of obtaining such a monohydrate by the hydrolysis of the starting trimethylsilyl ether disclosed therein. See Working Example 1. Fluconazole monohydrate is not a new compound as is evidenced in the last paragraph of the background portion of the present application where GB 2270521 is cited for disclosing the synthesis of fluconazole monohydrate from anhydrous fluconazole. Applicants are now making a copy of GB 2270521 of record in the present application.

According to page 10, first full paragraph of the present application, the fluconazole monohydrate obtained by the hydrolysis of the starting silyl ether of the Formula (II) is extremely pure. No one has ever before prepared fluconazole monohydrate in such highly pure form and because this highly pure form of fluconazole monohydrate is novel and contributes to the success of the present invention, to obtain highly pure fluconazole, the hydrolysis step of claim 1 is patentably distinguishable over ITOH et al per se or in combination with the other cited references. Claim 1 as presented in this application is broad enough to cover the hydrolysis of the Formula (II) silyl ether to obtain fluconazole monohydrate per se as well as the combination of this hydrolysis with any of four process variants (a) through (d) to obtain fluconazole Modification I by

rapid cooling, fluconazole Modification II by slow cooling, fluconazole Modification II by seeding with fluconazole Modification II crystals or fluconazole Modification I by seeding with fluconazole Modification I crystals.

The British Patent 2,270,521 describes a process for preparing fluconazole monohydrate from anhydrous fluconazole not from a trimethylsilylether of fluconazole. The reference process includes dissolving the anhydrous fluconazole in hot water and crystallizing the monohydrate by cooling the saturated solution. The obtained fluconazole monohydrate has a melting point of 138°C. The reference does not contain any data concerning the purity of either the starting material or the obtained fluconazole monohydrate. However, the starting anhydrous fluconazole is known to contain significant impurities as will be discussed hereinafter, and since there has been no purification of the starting anhydrous fluconazole, there would be no reason to expect that the fluconazole monohydrate would be pure either.

Applicants believe that the pure fluconazole monohydrate having a melting point of 139° to 140° C and obtained in high purity through the presently claimed hydrolysis of the trimethylsilylether of the Formula (II) is an integral part of the present invention and so Applicants have added claim 11 directed to fluconazole at the higher melting point than is disclosed in British Patent 2,270,521.

Claim 11 is believed to be patentably distinguishable over all of the cited prior art.

None of the remaining references cited by the Examiner taken alone or taken cumulatively in combination with ITOH et al provides any basis to reject any claim now presented as obvious under 35 USC 103. GUI et al deals with the experimental identification of the two polymorphs of fluconazole and discloses some physical data for same. There is no disclosure in the reference of how to prepare fluconazole in any form and no disclosure of fluconazole monohydrate in any form or the preparation thereof. Thus this reference taken alone or together with ITOH et al provides no basis to reject any claim now presented as obvious under 35 USC 103.

The KREIDL et al reference discloses silyl ethers of fluconazole and analogous compounds. The silyl ethers possess high antifungal activity and can be used as active ingredients in antifungal pharmaceutical compositions. The compounds were deemed to be stable based upon the experimental data disclosed in col. 5, lines 23 to 30. There is no disclosure of any process to prepare fluconazole or fluconazole monohydrate to be found in this reference. Thus this reference taken alone or together with ITOH et al and GUI et al provides no basis to reject any claim now presented as obvious under 35 USC 103.

The CLIVE et al reference discloses processes to prepare intermediates used in the preparation of fluconazole. There is no disclosure or suggestion of preparing fluconazole by hydrolysis of the trimethylsilyl ether and no disclosure of the formation of fluconazole monohydrate. Thus this reference taken alone or together with ITOH et al, GUI et al and KREIDL et al provides no basis to reject any claim now presented as obvious under 35 USC 103.

Applicants are making of record a copy of US Patent 4,404,216 which is equivalent to British Patent 2,099,818 already of record. According to col. 4, lines 10 to 20 of US Patent 4,404,216, it is disclosed that the chemical reaction between the oxirane compound of the Formula (II) and the 1,2,4-triazole produces an "unwanted isomeric version" as a contaminant. The unwanted isomer version must be removed from the obtained fluconazole or else by recrystallization, Formation of the isomeric impurity can be traced back to the fax that in this reaction the activity of the nitrogen atoms in positions 1 and 2 are equivalent, and produce the same final compound fluconazole. But the reaction of the nitrogen atom in position 4 produces the unwanted isofluconazole contamination. As only two nitrogen atoms are available to produce the good fluconazole, but one nitrogen atom is available to produce the undesired isofluconazole, the amount of the latter that is produced versus the former is considerable.

The examples show in the present assignee's previous patent, US Patent 5,707,976, that the trimethylsilyl ether of fluconazole can be produced in very high yields. In the process claimed in this patent the reagent is 1-(trimethyl-silyl)-1,2,4-triazole. In this reaction the heterocyclic nitrogen atom in position 1 of the 1,2,4-triazole is the one that will react with the epoxy group of the other reactant, as opposed to the 4-position heterocyclic nitrogen. That is why the obtained trimethylsilyloxy-fluconazole is practically free from the isofluconazole impurities. With a base catalyzed hydrolysis of the obtained pure trimethylsilyloxy-fluconazole, a solution of very pure fluconazole can be obtained, from which, without further purification steps, a very pure fluconazole monohydrate is obtained with a melting point of 139° to 140° C. As the drying of the fluconazole monohydrate under the stated conditions does not attack the fluconazole, the obtained crystalline polymorphic forms of fluconazole are highly pure as well.

In order to establish that Applicants' presently claimed process with its highly pure trimethylsilyloxy-fluconazole starting material of the Formula (II) obtained according to the process disclosed in the KREIDL et al reference results in obtaining fluconazole monohydrate in very high purity and in obtaining the anhydrous fluconazole in very high purity, Applicants have carried out HPLC on all three of these products. The results are presented in a declaration under 37 CFR 1.132 that accompanies this amendment. The results show that the highly pure trimethylsilyloxy-fluconazole

starting material of the Formula (II) contains very small amounts of the isofluconazole, designated as Impurity A, in the form of its trimethylsilyl ether and very small amounts of 2-[2-fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol, designated as Impurity B, in the form of its trimethylsilyl ether. Similarly the results show that the fluconazole monohydrate and anhydrous fluconazole obtained also have very small amounts of these same impurities. However, when the Pharmeuropa from 1998 was consulted (excerpt attached to the declaration) to provide the amount of these same impurities conventionally found in fluconazole monohydrate and anhydrous fluconazole commercially available, it was found that several times more of these impurities existed in the form of the free alcohol, not the trimethylsilyloxy ethers thereof. Thus here is proof of the surprisingly high purity of both the fluconazole monohydrate intermediate and the anhydrous fluconazole final proiduct in either crystal polymorph Form I or Form II.

Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

Respectfully submitted,
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Enc: Declaration under 37 CFR 1.132
PTO Form 1449 and References

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